REMARKS

Pending claims are 31-36. Reconsideration of the newly-stated rejection of these claims under 35 U.S.C. 103 is requested in view of the following comments.

The subject matter claimed in claims 31-36 is a composition which comprises a modified mRNA which encodes a human tumor antigen, wherein the mRNA has an increase in Guanine/Cytosine (GC) content relative to the GC content of the wild-type mRNA encoding the same antigen ("GC enriched mRNA").

Claims 31-36 are rejected on the ground that the claimed subject matter would have been obvious from Felgner et al. in view of Zhou et al., Adema et al., Nagata et al., and Foomsgaard.

Zhou and Adema have been cited in the new rejection for disclosing gp100 antigen nucleic acid. While gp100 is a human tumor antigen within the scope of claims 31-36, the combined teachings of Felgner, Zhou and Adema do not suggest to enrich the GC content or gp100 (or any other human tumor antigen) in the context of an RNA vaccine. The newly-cited Adema patent, summarized on page 5 of the Official Action, contemplates modifications of nucleic acid based on the degeneracy of the genetic code (e.g. col. 4, lines 52-60), but does not suggest GC enrichment.

The crux of the rejection relies upon Nagata and Foomsgaard as evidence of motivation to enrich GC content and as providing an expectation of higher expression of mRNA and improved immunogenicity. Official Action, page 8, 1st full paragraph; page 11, lines 6-11; page 12, last 4 lines; page 18, lines 15-21. Applicants urge reconsideration of this point.

Nagata et al. and Foomsgaard are cited as providing motivation to improve the expression and immunogenicity of human tumor antigens, yet, neither reference relates to human tumor antigens, and in fact, both references expressly relate to expression of non-human genes in human cells. As explained on the record previously, that is a distinct technical problem from the utility addressed by the present invention (expression of human tumor antigens in human cells *in vivo* to provide an immune response in a human host).

Specifically, Nagata *et al.* address the problem of obtaining high level expression of genes from microorganisms in mammalian cells. Page 445, left column. The experiments were conducted with antigens from Listeria and Plasmodium. Page 446, left column, 1st paragraph. Those antigens were selected specifically because their codon bias is different from that of human genes. Page 450, left column, 1st paragraph under "Discussion." There is no disclosure in Nagata *et al.* which suggests the desirability of enriching the GC content of human genes for expression in human cells.

Foomsgaard is focused upon a DNA vaccine against HIV (a human pathogen). Foomsgaard provides no suggestion to enrich the GC content of any autologous gene, and does not mention a composition including an mRNA encoding a human tumour antigen. There is no disclosure in Foomsgaard which suggests the desirability of enriching the GC content of human genes for expression in human cells.

It is respectfully submitted that the primary references (considered as Felgner, Zhou and Adema) are not properly combinable with the secondary references (Nagata and Foomsgaard) to find obviousness. As noted, the skilled artisan contemplating Felgner, Zhou and Adema is provided with no suggestion to use a modified mRNA which is GC enriched. The secondary references to Nagata and Foomsgaard are unrelated to anti-tumour therapy, and are directed solely to enhancing expression in human cells of antigens from particular non-human pathogenic infectious agents. Since the technical problems being addressed by the two sets of references are distinct, the cited references when considered cumulatively do not reasonably suggest the claimed "pharmaceutical compositions," absent hindsight. For this reason, the new rejection should be withdrawn for the same reason that the previous rejection based on Felgner in view of Chen and Foomsgaard was withdrawn - the references considered in proper combination do not make out *prima facie* obviousness.

Certain additional points are made below in response to specific statements which appear in the Official Action.

On page 8, the Official Action refers to Figure 1 and explains that when gp100 is modified with the preferred codons of Foomsgaard, the GC content is maximized. In response, this line of argument is premised upon the recognition that the codon usage of the wild-type gene is not optimized according to the codon usage disclosed by Foomsgaard. This statement of the issue reflects a hindsight use of the key finding which underlies the present invention, i.e. that human genes are not expressed in the most efficient way possible and that human gene expression may be enhanced by GC modifications. This key recognition is not provided by either the gp100 prior art or by Foomsgaard's disclosure relating to expression of non-human pathogenic genes.

On the bottom of page 13, the Official Action finds unpersuasive the argument that Chen and Foomsgaard disclose only heterologous antigens (which is equally true of the newly-cited Nagata article). The Official Action states: "There is no reason that one would not have applied the technique of codon optimization to human genes to be expressed in human cells." In response, Applicants submit that a factual foundation for a conclusion of obviousness requires a reason in the prior art to make the claimed invention, not the absence of any reason why the invention could not have been made. A legally correct obviousness analysis remains focused on what was suggested by the prior art, not what was possible.

The Official Action concludes at the bottom of page 16: "One would have been motivated to eliminate rare codons and optimize preferred codons of any sequence, even a human sequence, to improve translation in human cells." In response, the cited Nagata and Foomsgaard references do not support the breadth of that statement, since those references do not address "any sequence." There is no articulated basis on the record for why the skilled artisan would have seen any need to modify a human RNA (in particular, a human tumor antigen RNA) for expression in human cells. To the contrary, Applicants' citation to the Robinson article confirms that the state of the art, even subsequent to the present invention, was conflicted over whether such changes were even relevant to human genes.[1] Given this state of the art, it is

[1] For reference, the relevant passage of Robinson cited in the prior response is reproduced here: "Despite the recognized variability in codon content of human genes... little attention has been focused upon the possibility that expression of human proteins might be limited in human

not surprising that the prior art fails to teach GC enrichment of human genes in the context of a human expression system.

The Official Action makes several points relative to expression and immunogenic effect, to which Applicants would like to respond.

On page 16, lines 7-8, the Official Action states that no "objective evidence" has been provided that in vitro expression does not correlate with *in vivo* expression. In response, the cited Robinson article has been cited as objective evidence for what persons in the art believed, and confirms art recognition that "[t]he extent to which codon bias influences gene expression *in vivo* remains an open question."

On page 16, the Official Action states that evidence relating to Survivin, gp100, TRP-2, MAGE-A2, MAGE-C2 and STEP is not commensurate with the claims. In response, no reasoning has been offered why the evidence associated with the use of these six different human tumor antigens is not commensurate with the claim scope.

Applicants have a fundamental disagreement with the rationale in the Official Action concerning the predictability/unpredictability of the art. On page 17, the Official Action points to the prior argumentation concerning enablement and the associated evidence of predictability, to suggest that Applicants cannot now argue unpredictability. In response, the standards for enablement under Section 112 and the standards for patentability under Section 103 are distinct.[2]

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cells by the codon content of their mRNAs. On the contrary, there appears to have been a widespread tacit assumption that even though some human ORFs may have an unusually low G+C content in the wobble positions, the deviation from average is not so extreme as to restrict protein expression due to limiting cognate tRNA availability."

[2] See, e.g. *Gen-Probe Inc. v. Vysis, Inc.*, 2002 WL 34413199 (S.D.Cal. 2002) (vac'd other grounds), 70 U.S.P.Q.2d 1087 (Fed. Cir. 2004) ("Obviousness under § 103 focuses on three major factual inquiries: (1) the level of skill in the art, (2) the disclosures and content of the prior art and (3) whether the "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious...." ... The inquiries for lack of enablement occur under a different legal standard. The enablement inquiry under § 112 focuses on the disclosure in the specification and on whether 'the specification ...

What is possible without undue experimentation based upon a disclosure, and what would have been suggested by the prior art, are not necessarily overlapping in scope.

Specifically to the present facts, what was demonstrated to be enabled in the 1/28/08 response can be considered as a basal level of genetic vaccine utility - the prior art recognized that genetic vaccines have utility and disclosed generally how to make and use them. On that basis, the claimed subject matter was found to be enabled, and the rejection under Section 112, 1st paragraph was withdrawn. A totally different question is posed in connection with 35 U.S.C. 103, namely, whether the increased immunogenic activity of GC modified RNA relative to unmodified RNA reported by Dr. Hoerr's declaration would have been expected. Permitting Applicants to clarify their position, the complexity of the involved intracellular processing mechanisms (reproduced on pp. 16-17 of the Official Action) was intended to show that the observed increase in immunogenic response would not have been predictable.

Based on the foregoing, claims 31-36 are patentable under 35 U.S.C. 103 and prompt allowance is requested.

A fee for a one-month extension of time is due with this response. However, if any additional fee is due, please charge our Deposit Account No. 03-2775 under Order No. 22122-00009-US1 from which the undersigned is authorized to draw.

Dated: April 20, 2009

Respectfully submitted,

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contain[s] a written description of the invention, and of the manner and process of making and using it ... to enable any person skilled in the art ... to make and use the same....'") (citations omitted).